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**Published**

*With international search report.*

(54) Title: ANTIHYPERTENSIVE MEDICAMENTS CONTAINING LACIDIPINE AND TELMISARTAN

(57) Abstract

Combinations comprising diethyl (E) -4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate(lacidipine) and 4'-[[2-n-propyl-4-methyl-6-(1-methylbenziimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid (telmisartan), pharmaceutical compositions containing said combinations and their use in the treatment of cardiovascular disorders including hypertension.

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# ANTIHYPERTENSIVE MEDICAMENTS CONTAINING LACIDIPINE AND TELMISARTAN

The present invention relates to therapeutic combinations comprising diethyl (E) –4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate(lacidipine) and 4'-[[2-n-propyl-4-methyl-6-(1-methylbenziimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid (telmisartan), to pharmaceutical compositions containing said combinations and their use in the treatment of cardiovascular disorders including hypertension.

Lacidipine, which is described in British patent no. 2164336 , is a potent long acting calcium antagonist which is particularly useful for treating hypertension. The compound may be also useful for the treatment of other cardiovascular disorders including atherosclerosis, peripheral vascular disease, ischaemic heart disease and congestive heart failure.

Telmisartan, which is described in European patent no. 0502314, is an angiotensin-II-antagonist which is useful for treating hypertension and cardiac insufficiency and for treating other cardiovascular disorders including ischaemic peripheral circulation disorders, myocardial ischaemia (angina).

European patent no. 0502314 teaches that the angiotensin-II-antagonists described therein may be administered in combination with other active substances including calcium antagonists. There is however no specific disclosure of such combinations with lacidipine.

We have found that the combination of lacidipine and telmisartan provides a useful and unexpectedly advantageous combination for the treatment of cardiovascular disorders, such as hypertension, atherosclerosis and ischaemic heart disease.

In particular it has now been found that by combining lacidipine and telmisartan, a synergistic antihypertensive effect is achieved.

It is a feature of this invention that the use of such a drug combination will provide one or more of the following effects: synergistic antihypertensive effects, antihypertensive effect over a longer period and/or allow a better management of any potential drug-related side effects.

Furthermore, the improvement of blood pressure control achieved by using such a drug combination may afford a better protection from the associated diseases which are induced by hypertension.

According to one aspect of the invention there is provided a combination comprising lacidipine and telmisartan or a physiologically functional derivative thereof and more particularly a combination comprising lacidipine and telmisartan.

As used herein, the term "*physiologically functional derivative*" includes any physiologically acceptable solvate, salt, ester, salt of such ester, or solvates of any such salt or ester, of telmisartan.

Preferred esters in accordance with the invention are independently selected from the following group: (1) carboxylic acid esters in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, n-propyl, t-butyl, or n-butyl), cycloalkyl, alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, $C_{1-4}$ alkyl, or $C_{1-4}$ alkoxy), or amino; (2) sulphonate esters, such as alkyl- or aralkylsulphonyl (for example, methanesulphonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); and (4) phosphonate esters. In such esters, unless otherwise specified, any

alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to a physiologically acceptable salt thereof.

Examples of physiologically acceptable salts include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and $NX_4^+$ (wherein X is $C_{1-4}$ alkyl) or

ammonium salts, formed with amino acids (e.g lysine and arginine) and organic bases (e.g procaine, phenylbenzylamine, ethanolamine and N-methyl glucosamine).

Salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

The present invention thus provides a method for the treatment of hypertension in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a combination of lacidipine and telmisartan or a physiologically functional derivative thereof.

Reference herein to treatment extends to prophylaxis as well as the treatment of established hypertension or symptoms.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same or different pharmaceutical formulations or sequentially. If there is sequential administration, the delay in administering the second and any subsequent active ingredient should not be such as to lose the benefit of a synergistic therapeutic effect of the combination of the active ingredients. It will also be understood that the compounds of the combination or the physiologically functional derivatives of any thereof, whether presented simultaneously or sequentially, may be administered individually or in multiples or in any combination thereof.

According to another aspect, the present invention provides the use of lacidipine in the manufacture of a medicament for administration simultaneously or sequentially with telmisartan or a physiologically functional derivative thereof for the treatment and/or prophylaxis of hypertension.

The synergistic effects of the combination of lacidipine and telmisartan may be seen over a wide ratio of combinations, for example, of 1: 100 to 1: 1, such as 1:50 to 1:2 (by weight), preferably of 1:40 to 1:3.33(by weight). Examples of such combinations include those wherein the ratio (by weight) of lacidipine to telmisartan is 1:5; 1:10, 1:20; 1:40; 1:6.67 or 1:13.33. Conveniently each compound will be employed in the combination in an amount at which it exhibits an antihypertensive effect when used alone.

The amount of a combination of lacidipine and telmisartan required to be effective as antihypertensive may, of course, vary and is ultimately at the discretion of the medical practitioner. The factors to be considered include the route of administration and nature of the formulation, the animal's body weight, age and general condition and the nature and severity of the disease to be treated.

In general a suitable dose of lacidipine for administration to a human for the treatment of hypertension may be in the range of 0.1 to 10 mg per day, preferably in the range of 1 to 6 mg per day and most preferably in the range 2-6 mg per day. Lacidipine is advantageously administered by oral route once a day.

In general, a suitable dose of telmisartan for administration to a human may be in the range of 5 to 120 mg per day, advantageously in the range of 20 to 80 mg per day. Telmisartan is advantageously administered by oral route once a day.

Unless otherwise indicated all weights of active ingredients are calculated in terms of the drug *per se*. The desired dose may preferably be presented as one, two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. Conveniently lacidipine and telmisartan are administered as a single daily dose.

The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner.

While it is possible for the active ingredients of the combination to be administered as the raw chemical it is preferable to present them as a pharmaceutical formulation. Pharmaceutical formulations according to the present invention comprise a combination according to the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. The carrier(s) must be acceptable in the

sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. When the individual components of the combination are administered separately they are generally each presented as a pharmaceutical formulation. The references hereinafter to formulations refer, unless otherwise stated, to formulations containing either the combination or a component thereof.

A combination of lacidipine and telmisartan or a physiologically functional derivative thereof may conveniently be presented as a pharmaceutical formulation in a unitary dosage form. A convenient unitary dosage formulation contains lacidipine in an amount from 1mg to 6 mg and telmisartan in an amount from 10 mg to 100 mg.

A particularly convenient unitary dosage formulation contains lacidipine in an amount from 2 mg to 6 mg, more particularly in an amount from 2mg to 4 mg, and telmisartan in amount from 20mg to 80 mg.

Pharmaceutical formulations are often prescribed to the patient in "patient packs" containing the whole course of treatment in a single package, usually a blister pack. Patient packs have an advantage over traditional prescriptions, where a pharmacist divides a patient's supply of a pharmaceutical from a bulk supply, in that the patient always has access to the package insert contained in the patient pack, normally missing in traditional prescriptions. The inclusion of a package insert has been shown to improve patient compliance with the physician's instructions and, therefore, lead generally to more successful treatment.

It will be understood that the administration of the combination of the invention by means of a single patient pack, or patient packs of each formulation,

containing within a package insert instructing the patient to the correct use of the invention is a desirable additional feature of this invention.

According to a further aspect of the invention provided is a multiple, for example, double or triple, pack comprising at least lacidipine and telmisartan or a physiologically functional derivative thereof and an information insert containing directions on the use of the combination of the invention.

Formulations include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods represent a further feature of the present invention and include the step of bringing into association the active ingredients with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, cachets or tablets each containing a predetermined amount of the active ingredients; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in

a suitable machine the active ingredients in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, sodium croscarmellose cross-linked povidone, cross-linked sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding a mixture of the powdered compound moistened with an inert liquid diluent in a suitable machine. The tablets may optionally be coated or scored any may be formulated so as to provide slow or controlled release of the active ingredients therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredients in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. Formulations for rectal administration may be presented as a suppository with a suitable base comprising, for example, cocoa butter or polyethylene glycols.

Topical administration may also be by means of a transdermal iontophoretic device.

Formulations suitable for vaginal administration may be presented as tablets, pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by admixture of the active combination with the softened or melted carrier(s) followed by chilling and shaping in molds.

Formulations suitable for parenteral administration include aqueous and nonaqueous isotonic sterile injection solutions which may contain anti-oxidants, buffers, preservatives and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents; and liposomes or other microparticulate systems which are designed to target the compound to blood components or one or more organs. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

The pharmaceutical composition of the invention containing the two active ingredients may be prepared according to conventional techniques well known

in the pharmaceutical industry. Thus, for example the lacidipine and telmisartan may be admixed together with suitable excipients such as those described above for the formulation of each of the active ingredients separately. Tablets may be prepared, for example by direct compression of such a mixture or using other conventional methods. Bilayer tablets may be prepared according to conventional procedure. Thus, for example, by separately compressing the two blends in a suitable tabletting machine with two filling stations. Capsules may be prepared by filling the blend along with suitable excipients into gelatin capsules, using a suitable filling machine. Controlled release forms for oral or rectal administration may be formulated in a conventional manner associated with controlled release forms.

**Biological data:**

The advantageous profile of antihypertensive activity obtained by the administration of lacidipine with telmisartan may be demonstrated in the male spontaneously hypertensive rats.

In this test lacidipine (0.2mg/kg), telmisartan (1mg/kg) and a combination of lacidipine (0.2mg/kg ) and telmisartan (1mg/kg) were administered as a suspension in 0.5% Methocel™ (Hydroxypropyl methyl cellulose) by oral gavage to male spontaneously hypertensive rats.

After dosing, mean blood pressure (MBP) and heart rate (HR) variations were calculated at fixed intervals and expressed as a percentage of pre-drug values. The results obtained three hours after administration of lacidipine and telmisartan, alone or in combination, are summarised below:

| | Compound | | |
|---|---|---|---|
| | lacidipine | telmisartan | lacidipine |

| | 0.2mg/kg | 1mg/kg | 0.2mg/kg telmisartan 1mg/kg |
|---|---|---|---|
| MBP | -13.8 ± 5.4 | -4.5 ± 8.2 | -30.5 ± 5.0 |
| HR | 1.9 ± 6.4 | 2.7 ± 17.0 | 12.6 ± 23.1 |

The reduction in mean blood pressure with the combination of lacidipine and telmisartan was significantly greater than was to be expected and this was also achieved without a significant effect on the heart rate. Duration of action studies also established that the antihypertensive effect of the lacidipine-telmisartan combination was clearly longer lasting than the effect induced by lacidipine and telmisartan alone.

The compounds of the combination of the present invention may be obtained in a conventional manner.

Lacidipine may be prepared by the method described in British Patent N° 2164336 which is incorporated herein by reference hereto.

Telmisartan or a physiologically functional derivative thereof may be prepared by the method described in European Patent N°502314 which is incorporated herein by reference or by known methods described for analogous compounds

For co-administration the lacidipine and telmisartan may be formulated in a conventional manner. Thus for example lacidipine may be formulated as described in British Patent N° 2164336 and telmisartan may be formulated as described in European Patent N° 0502314.

In a preferred aspect of the invention lacidipine and telmisartan are formulated in a single pharmaceutical composition.

In order that this aspect of the invention may be more fully understood the following examples are given by way of illustration only.

TABLET FORMULATIONS:

**Example 1**

The following formulation was prepared by mixing lacidipine granulated containing monohydrate lactose and telmisartan spray dried granulate with sorbitol, followed by addition of magnesium stearate and compression.

| | mg/tablet |
|---|---|
| Lacidipine | 4 |
| Telmisartan | 40 |
| Monohydrate Lactose | 197 |
| Sodium Hydroxide | 3.36 |
| Meglumine | 12 |
| Povidone | 52 |
| Sorbitol | 184 |
| Magnesium Stearate | 7.5 |

**Example 2**

The following formulation was prepared by mixing telmisartan spray dried granule with sorbitol and magnesium stearate. Then lacidipine granule was mixed with the remaining magnesium stearate and eventually with sorbitol. The

two blends were separetely compressed in a suitable tabletting machine with two filling stations to produce bilayer tablets.

| | mg/tablet |
|---|---|
| Telmisartan | 40 |
| Lacidipine | 4 |
| Povidone | 40 |
| Monohydrate Lactose | 197 |
| Sodium Hydroxide | 3.36 |
| Meglumine | 12 |
| Povidone | 12 |
| Sorbitol | 184.1 |

The following formulations (Examples 3a-3d) may be prepared by mixing a granulate containing lacidipine, sorbitol and povidone with telmisartan spray dried granulate, sorbitol, followed by addition of magnesium stearate and compression.

**Example 3a**

| | mg/tablet |
|---|---|
| Telmisartan | 40 |
| Lacidipine | 4 |
| Povidone | 52 |

| | |
|---|---|
| Sorbitol | 116 |
| Sodium Hydroxide | 3.36 |
| Meglumine | 12 |
| Sorbitol | 117.64 |
| Magnesium Stearate | 5 |

**Example 3b**

| | mg/tablet |
|---|---|
| Telmisartan | 20 |
| Lacidipine | 2 |
| Povidone | 26 |
| Sorbitol | 138 |
| Sodium Hydroxide | 1.68 |
| Meglumine | 6 |
| Sorbitol | 151.32 |
| Magnesium Stearate | 5 |

**Example 3c**

| | mg/tablet |
|---|---|
| Telmisartan | 80 |
| Lacidipine | 2 |
| Povidone | 44 |
| Sorbitol | 138 |

| | |
|---|---|
| Sodium Hydroxide | 6.72 |
| Meglumine | 24 |
| Sorbitol | 50.28 |
| Magnesium Stearate | 5 |

**Example 3d**

| | mg/tablet |
|---|---|
| Telmisartan | 80 |
| Lacidipine | 6 |
| Povidone | 84 |
| Sorbitol | 94 |
| Sodium Hydroxide | 6.72 |
| Meglumine | 24 |
| Sorbitol | 50.28 |
| Magnesium Stearate | 5 |

**Example 4**

The following formulation was prepared by granulating telmisartan spray dried granule and sorbitol with lacidipine and povidone followed by addition of sorbitol and magnesium stearate and compression.

| | mg/tablet |
|---|---|
| Lacidipine | 4 |
| Povidone | 40 |

| | |
|---|---|
| Sorbitol | 88.64 |
| Telmisartan | 40 |
| Sodium Hydroxide | 3.36 |
| Meglumine | 12 |
| Povidone | 12 |
| Sorbitol | 295 |
| Magnesium Stearate | 5 |

## CLAIMS

1. A combination comprising diethyl (E) –4-[2-[(tert-butylcarbonyl)vinyl]phenyl-1,4-dihydro-2,6-dimethylpyridine-3,5 dicarboxylate (lacidipine) and 4'-[[2-n-propyl-4-methyl-6-(1-methylbenziimidazol-2-yl)-benzimidazol-1-yl]-methyl]-biphenyl-2-carboxylic acid (telmisartan) or a physiologically functional derivative thereof.

2. A combination according to claim 1 for use in medical therapy.

3. A combination according to claim 1 for use in the treatment and or prophylaxis of hypertension.

4. A combination according to claim 1 wherein the ratio of lacidipine to telmisartin is from 1:100 to 1:1 by weight.

5. A method for the treatment of hypertension in a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a combination of as claimed in claim 1.

6. A method according to claim 5 wherein the combination is administered as a single combined formulation.

7. A pharmaceutical formulation comprising a combination according to claim 1 together with one or more pharmaceutically acceptable carriers or excipients.

8. A pharmaceutical formulation according to claim 7 in unit dosage form.

9. The use of lacidipine in the manufacture of a medicament for administration simultaneously or sequentially with telmisartan or a physiologically functionally derivative thereof for the treatment and/or prophylaxis of hypertension.

10. A patient pack comprising lacidipine and telmisartan or a physiologically functional derivative thereof.

# INTERNATIONAL SEARCH REPORT

Inte. ɔnal Application No
PCT/GB 98/03336

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | EP 0 502 314 A (THOMAE GMBH DR K)<br>9 September 1992<br>cited in the application<br>see page 20, line 46 - page 21, line 6;<br>claims 1,5,8<br>--- | 1-3,5-10 |
| Y | WO 96 07400 A (ASTRA AB) 14 March 1996<br>see page 6, line 4-22<br>see page 7, line 4-5; claims 1,5-13,21-27<br>--- | 1-10 |
| Y | WO 96 19233 A (OMEROS MED SYS INC)<br>27 June 1996<br>see page 9, line 7-25; examples 4-6<br>see page 10, line 11-20<br>see page 28, line 5 - page 31, line 4<br>---<br>-/-- | 1-10 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 2 July 1999 | 12/07/1999 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Kanbier, D |

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Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 98/03336

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 97 36874 A (SMITHKLINE BEECHAM CORP)<br>9 October 1997<br>see page 7, line 30 - page 8, line 9;<br>claims 11,16,17 | 1-10 |
| A | WO 98 40067 A (SANOFI SA)<br>17 September 1998<br>see page 10, line 11 - page 11, line 22 | 1-10 |
| A | WO 98 30216 A (MERCK & CO INC)<br>16 July 1998<br>see claims | 1 |

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03336

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-10
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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